The long-term cost-effectiveness of clopidogrel plus aspirin in patients undergoing percutaneous coronary intervention in Sweden
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined percutaneous coronary intervention (PCI) with clopidogrel plus aspirin versus aspirin alone in patients with unstable coronary artery disease (CAD).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients undergoing PCI. Patients who had undergone a revascularisation procedure within 3 months or who had received treatment with glycoprotein IIb/IIIa inhibitors 3 days before randomisation were excluded, as were patients contraindicated for antithrombotic therapy and those suffering from Class IV heart failure. Further details can be found in another publication (Mehta et al. 2001, see 'Other Publications Of Related Interest' below for bibliographic details).

Setting
The setting was secondary care. The economic evaluation was conducted in Sweden.

Dates to which data relate
The main data for this model-based economic evaluation were retrieved from a Swedish national registry from 1 January 1995 to 1 August 2001 and the PCI CURE study (Mehta et al. 2001). The price year was 2004.

Source of effectiveness data
This study mainly used two sources of data, namely a review of the literature and estimates.

Modelling
A four-state Markov Model was constructed to estimate the long-term costs and effectiveness. The states within the model were after PCI (the starting state for all patients), first year after a myocardial infarction (MI), the second and subsequent years after an MI, and death. The model used yearly cycles.

Outcomes assessed in the review
The outcomes assessed in the non-systematic review were the risk reduction from treatment and the utility reduction from MI.
Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
The authors stated that MEDLINE was searched when looking for utility data. The search was conducted from 1980 to 2003 using the search terms "utility", "quality of life" and "myocardial infarction".

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Only one study was used as source of effectiveness data (Mehta et al. 2001).

Methods of combining primary studies
Not applicable (only one study was used).

Investigation of differences between primary studies
Not applicable (only one study was used).

Results of the review
The risk reduction from treatment was 0.72 (95% confidence interval, CI: 0.53 to 0.96).

The utility reduction due to MI was 0.1.

Methods used to derive estimates of effectiveness
The authors derived estimates of effectiveness by means of regression analyses, using data from a national registry that included patients undergoing PCI.

Estimates of effectiveness and key assumptions
Coefficients for the risk functions used to calculate transition probabilities in the model were as follows.

For cardiovascular death or nonfatal MI for first year after MI: constant -6.761, age 0.057 (95% CI: 0.042 to 0.0738), diabetic 0.552 (95% CI: 0.188 to 0.915) and previous MI 0.220 (95% CI: -0.136 to 0.577).

For cardiovascular death or nonfatal MI in subsequent year after MI: constant -8.185, age 0.054 (95% CI: 0.018 to 0.090, diabetic 0.667 (95% CI: -0.026 to 1.308) and previous MI 0.621 (95% CI: 0.058 to 1.184).

For cardiovascular death: constant -6.417, age 0.081 (95% CI: 0.051 to 0.111), diabetic 0.1656 (95% CI: -0.498 to 0.830) and previous MI 0.289 (95% CI: -0.338 to 0.915).

For death due to other causes: constant -8.442, age 0.0646 (95% CI: 0.046 to 0.083), diabetic 0.462 (95% CI: 0.029 to 0.895) and previous MI 0.365 (95% CI: -0.012 to 0.741).
Measure of benefits used in the economic analysis
The measure of effectiveness used was the life-years gained (LYG).

Direct costs
The authors used diagnosis-related groups as proxies for resource use. These were mainly health care costs. The authors used these to calculate the initial hospitalisation cost-difference between study groups in their model. They also included the cost of MI obtained from the literature (e.g. inpatient and outpatient care, pharmaceuticals and loss of productivity (work absence), but not the patient's own expenditures). Subsequent costs were also obtained from the literature. All costs were adjusted for inflation using a consumer price index and were presented in 2004 euros. Discounting was carried out using a 3% rate, as recommended by Swedish guidelines for economic evaluations.

Statistical analysis of costs
The costs were treated stochastically. For each arm of the study the authors presented the mean direct costs, as well as the indirect and total costs, with their standard deviations (SDs). Uncertainty around the costs was addressed using 1,000 bootstrap replications.

Indirect Costs
The study included the indirect costs due to MI, which were obtained from the literature. For their model, the authors used an indirect cost for the first year after MI and for subsequent years. These costs were expressed in 2004 euros and were discounted at a rate of 3%, as recommended by Swedish guidelines for economic evaluations.

Currency
Swedish kroner (SEK). These were converted to euros (EUR) at an exchange rate of EUR 1.00 = SEK 9.13.

Sensitivity analysis
Sensitivity analyses were performed. Variability in the data was investigated. The authors conducted one-way, sub-group and probabilistic sensitivity analyses (cost-effectiveness acceptability curves). Assumptions were made, based on the literature, (e.g. costs due to increased survival), in order to define ranges for the sensitivity analysis. A deterministic sensitivity analysis was conducted on costs for the first year after an MI, costs of the second year, costs associated with added years of life, discounting, and MI occurring within 7 days of hospital admission.

Estimated benefits used in the economic analysis
For the base-case analysis (whole population), the LYG were 0.04 (SD=0.05).
For the sub-group analyses, the LYG were:

- with diabetes mellitus, 0.03 (SD=0.05) at age 50 years, 0.04 (SD=0.06) at age 60 years, 0.05 (SD=0.08) at age 70 years, and 0.09 (SD=0.11) at age 80 years; and
- with no diabetes mellitus, 0.03 (SD=0.03) at age 50 years, 0.04 (SD=0.04) at aged 60 years, 0.05 (SD=0.06) at age 70 years, and 0.09 (SD=0.09) at age 80 years.

Cost results
The direct costs were EUR 2,277 (SD=1,478) for patients receiving aspirin and EUR 2,726 (SD=1,220) for patients receiving clopidogrel plus aspirin.
The indirect costs were EUR 523 (SD=174) for patients receiving aspirin and EUR 282 (SD=179) for patients receiving
clopidogrel plus aspirin.

The total costs were EUR 2799 (SD=1,494) for patients receiving aspirin and EUR 3,132 (SD=1,253) for patients receiving clopidogrel plus aspirin.

Synthesis of costs and benefits
The authors calculated the incremental cost-effectiveness ratios (ICERs). For the base-case analysis, the ICER was EUR 10,993/LYG when only the direct costs were included and EUR 8,127/LYG when both the direct and indirect costs were included.

For the sub-group analyses, the ICERs were:
with diabetes mellitus, dominance at age 50 years, EUR 1,969/LYG at age 60 years, EUR 7,213/LYG at age 70 years, and EUR 3,961/LYG at age 80 years; and
with no diabetes mellitus, EUR 7,243/LYG at age 50 years, EUR 6,929/LYG at age 60 years, EUR 7,937/LYG at age 70 years, and EUR 4,609/LYG at age 80 years.

The authors reported that the inclusion of MIs that occurred within 7 days of admission had a substantial effect on the results.

Authors' conclusions
Treatment with clopidogrel plus aspirin, as in the PCI CURE study, appears to have been cost-effective in this model analysis of patients with unstable coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) in Sweden.

CRD COMMENTARY - Selection of comparators
The authors chose the comparator for their analysis on the basis of those compared in a previous study (Mehta et al. 2001). You should decide if this represents a relevant technology in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness was calculated by means of a Markov model, using data from a single study and estimates derived using data from a national registry. The authors did not report a systematic review of the literature. Although this is common practice with models, it does not always ensure that the best available data are used in the model. The authors could have explored other sources for the treatment risk reduction variable.

Other risks of events were derived using regression analyses, i.e. logistic regression models. The authors stated clearly how they developed these and reported the results of the analyses. However, they did not report statistics for the regression models and, as such, it is not possible to know, for instance, how well these models behaved. However, the authors appropriately investigated the input estimates using one-way and probabilistic sensitivity analyses.

Validity of estimate of measure of benefit
The authors used the LYG as their effectiveness measure, but used quality-adjusted life-years (QALYs) within their sensitivity analyses. Although the authors searched MEDLINE, they found no useable estimates on the reduction in quality of life after an MI for the study population. They therefore used an assumed reduction in quality of life of 0.1, as used in a previous study, and acknowledged this as a limitation of their study.

Validity of estimate of costs
The authors conducted their analysis from a societal perspective. All the cost categories (e.g. direct and indirect) relevant to this approach seem to have been included in the analysis, as were all relevant costs within each category. The
costs were treated stochastically within the Markov model. The price year was reported. The authors did not report the resource quantities and the unit costs separately, which could make it difficult to rework the analysis in other settings and therefore limit the transferability of the results.

Other issues
The authors compared their findings with those from other studies which, in general, showed similar results. They did not explicitly address the issue of the generalisability of their results, but they did discuss the effects of some of the data used in the model that were particularly different from those used in other studies. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

A number of limitations were reported. For example, the cost data were old and based on a small sample. However, the authors conducted sensitivity analyses on these variables and found their results to be robust. Another limitation was the use of inclusion/exclusion criteria from a prior study that had not enrolled patients with previous PCI or coronary artery bypass graft. The authors pointed out that this could have led to an underestimate of the risk of an event in the model. A further limitation was the lack of data on QALYs since good QALY data would have enhanced the analysis.

Implications of the study
The predicted cost-effectiveness ratios are well below the willingness-to-pay thresholds generally considered cost-effective.

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Other publications of related interest
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Subject indexing assigned by NLM

MeSH
Aged; Aged, 80 and over; Angioplasty, Balloon, Coronary; Aspirin /administration & dosage /economics /therapeutic use; Computer Simulation; Coronary Disease /economics /therapy; Cost-Benefit Analysis; Drug Administration Schedule; Drug Costs; Drug Therapy, Combination; Female; Humans; Logistic Models; Male; Markov Chains; Middle Aged; Models, Economic; Monte Carlo Method; Platelet Aggregation Inhibitors /administration & dosage /economics
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